TRIAL STATISTICAL ANALYSIS PLAN

c24219582-01

BI Trial No.:	0248-0686
Title:	A two- stage multicenter, open-label, randomized, active controlled parallel group study comparing the efficacy and safety of Pramipexole SR versus Pramipexole IR administered orally over an 18-week treatment on nocturnal symptoms in L-Dopa+ treated patients with advanced Parkinson's disease (PD)
Investigational Product(s):	Pramipexole dihydrochloride monohydrate
Responsible trial statistician(s):	Phone:
Date of statistical analysis plan:	25 Sep 2019 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADL	Activities of Daily Living
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BMI	Body mass index
COMT	Catechol-O-Methyltransferase
CRF	Case Report Form
CT	Concomitant Therapy
CTL	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DBP	Diastolic Blood Pressure
DDC	Dopa-Decarboxylase
ECG	Electrocardiogram
EMO	Early Morning Off
EoT	End-Of-Text
ESS	Epworth Sleepiness Scale
EX	Exclusion criteria
FAS	Full Analysis Set
L-Dopa	Levodopa
L-Dopa^{+}	Levodopa combined with a Dopa-Decarboxylase-inhibitor
LLT	Lowest Level Term
ICH	International Conference On Harmonisation
IN	Inclusion criteria
IR	Immediate Release
MAO	Monoamine Oxydase
MedDRA	Medical Dictionary For Regulatory Activities
MMIDI	Modified Minnesota Impulsive Disorders Interview
MMSE	Mini-Mental State Examination
MQRM	Medical Quality Review Meeting
Min	Minimum
Max	Maximum
N	Number
NHQ	Nocturnal Hypokinesia Questionnaire
OC	Observed Case
PD	Parkinson’s Disease
PDSS-2	Parkinson’s Disease Sleep Scale 2nd version
PDQ	Parkinson's Disease Questionnaire

Term	Definition / description
ADL	Activities of Daily Living
PN	Preferred Name
PD	Protocol Deviation
PPS	Per Protocol Set
PR	Pulse Rate
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
RPM	Report Planning Meeting
SAS®	Statistical Analysis Software®
SBP	Systolic Blood Pressure
SD	Standard Deviation
SR	Sustained Release
SMQ	Standardised MedDRA Query
SOC	System Organ Class
ToC	Table of Contents
TMW	Trial Medical Writer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

The TSAP is used for the two-stage study to contain the overall analysis specification. But there may be some modifications if this study continues to Stage II.

SAS® Version 9.4 (or later) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No change concerning statistical analysis has occurred since the CTP was finalized.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Please refer to Sections 2.1.2 and 5.1 of the CTP.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable, since there are no key secondary endpoints specified in the protocol.

5.2.2 Secondary endpoint(s)

Secondary endpoints are described in sections 2.1.3 and 5.1 of the CTP.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

The definition below of the analysing treatment will be used for reporting of treatment emergent (On-Treatment) adverse events and to differentiate Screening and Post-Treatment safety data. The same labels and sort order as for the randomized treatment groups will be used.

- Screening: All adverse events occurring between informed consent and first drug intake will be assigned to 'screening' (for listings only).

Table 6.1: 1 Definition of analyzing treatments: Screening

Label	Sort order	Start date	Stop date
Screening		Date of informed consent	Date of first administration

- On-Treatment (i.e., 'Active + 2 days'): All adverse events occurring between first drug intake till 2 days after last drug intake will be assigned to 'On-treatment'.

Table 6.1: 2 Definition of analyzing treatments: On-treatment

Label	Sort order	Start date	Stop date
PPX SR	01	Date of first administration of Pramipexole SR	Date of last administration of Pramipexole SR + 2 days
PPX IR	02	Date of first administration of Pramipexole IR	Date of last administration of Pramipexole IR + 2 days

Note: An adverse event will be assigned to an analysing treatment (trt) based on start date (trt) <= start date (AE) < stop date (trt).

- Post-Treatment: All adverse events occurring after last drug intake + ≥3 days will be assigned to 'Post-treatment' (for listings only).

Table 6.1: 3 Definition of analyzing treatments: Post-treatment

Label	Start date	Stop date
Post-Treatment	Date of last administration + 3 days	Date of last contact

6.2 IMPORTANT PROTOCOL DEVIATIONS

All patients with important deviations from the protocol will be listed (Appendix 16.2 of the CTR). The IN/EX numbers refer to the definition given in the CTP and CRF.

Patients with potentially important protocol deviations (PDs) will be identified based on Table 6.2: 1 and documented. The table defines the different categories of important PDs. The final column describes which PDs will be used to exclude patients from the different patient analysis sets. Patients are either excluded from "All" analysis sets, the Per Protocol analysis set (PPS) or "None" of the analysis sets.
The list of PDs in Table 6.2: 1 is considered a 'working' list, which is expected to be updated throughout the trial and finalized prior to the Database Lock (DBL). In any case, all important PDs will be tracked during the study at Medical Quality Review Meetings (MQRMs) or Reported Plan Meeting (RPM) to verify the quality of the inclusion and the conduct of the study.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1			
	A1.1	Not confirmed idiopathic PD or age less than 30 years at time of diagnosis	Refers to IN1, IN3	PPS
	A1.2*	Not have clinically relevant sleep disturbances (i.e. PDSS-2 total score < 18 at baseline)	Refers to IN5	PPS
	A1.3*	Not feel uncomfortable at night (i.e. the score of question 9 in PDSS-2 < 2 at baseline)	Refers to IN6	PPS
	A1.4*	Not have early morning off (i.e. the score <2 at baseline)	Refers to IN7	PPS
	A1.5*	Motor fluctuations: with less than 2 cumulative hours of off time every day during waking hours	Refers to IN8	PPS
	A2			
	A2.1	Neuro-psychiatrics disease	Refers to EX1, EX2, EX3	None
	A2.2	History of psychosis (except history of drug induced hallucinations)	Refers to EX4	None
	A2.3*	Serious sleep apnea hypopnea syndrome (i.e. the score of question 15 in PDSS-2 ≥ 3 at baseline)	Refers to EX11	PPS
	A2.4	Participation in another clinical trial within one month or five time the ½ life of the investigational product	Refers to EX22	PPS
B		**Informed consent**		
	B1	Informed consent not available	Refers to IN13	All
	B2*	Informed consent too late	Refers to IN13	None
C		**Trial medication and randomization**		
	C1	Incorrect trial medication taken	Change in medication number during the trial (**)	PPS
	C3	Non-compliance		

Category / Code		Description	Requirements	Excluded from
	C3.1*	Overall compliance lower than 80% or higher than 120%	Treatment compliance	PPS

Table 6.2: 1 cont. Important protocol deviations

Category / Code		Description	Requirements	Excluded from
	C3.2*	Treatment stopped before 12 weeks ± 3 days(***)	Treatment duration	PPS
D		**Concomitant medication**		
	D1	**Improper medication prior to randomization**		
	D1.1*	Dopamine agonists (including pramipexole) within 4 weeks prior to randomization	Refers to IN11	PPS
	D1.2	Sustained release dopaminergic drug (i.e. sustained release Levodopa/DDC inhibitor) after supper, or any anti-PD medication after 9pm within 4 weeks prior to randomization	Refers to IN10	PPS
	D1.3	Any hypnotic medication within 4 weeks prior to the randomization	Refers to EX15	PPS
	D1.4	Medication with central dopamine antagonist activity within 4 weeks prior to randomization	Refers to EX16	PPS
	D2	**Prohibited medication use**		
	D2.1	Start of a prohibited medication during the trial (from screening to final visit for the analysis)	Refers to Section 4.2.2.1 in CTP	PPS
	E	**Missing primary endpoint data**		
	E1*	Patient has baseline PDSS-2 missing, or all maintenance period PDSS-2 missing		FAS

Note that for these important protocol deviations, there may be exceptions which will be discussed during the MQRM or RPM.
* IPDs will be identified programmatically.
** Unless the corresponding study treatment turns out to be identical.
*** Premature discontinuation will on technical level be handled as PD, although a premature discontinuation due to an AE does strictly speaking not “deviate” the protocol.

6.3 PATIENT SETS ANALYZED

CTP, Section 7 defined the patient sets used for analyses as below distinct Table 6.3: 1.

Table 6.3: 1 Patient sets analyzed

Class of endpoint	Patient set		
	Treated set (TS)	Full analysis set (FAS)	Per protocol set (PPS)
Primary endpoint		primary analysis	sensitivity analysis
secondary and further endpoints		X	
Safety endpoints	X		
Demographic/baseline endpoints	X		

The number of patients with available data for an endpoint may differ. For details, see Section 6.6.

6.5 POOLING OF CENTRES

This section is not applicable because center is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

For all efficacy scales, there is initially no intention to estimate missing efficacy data. However, depending on the amount and pattern of missing data detected during MQRMs, the decision for missing data imputation will be taken. This decision will be taken latest during the final Report Planning Meeting (RPM). If the choice is to replace missing items, then the rules described in section 6.6.1 will be applied.

6.6.1 Determination of Observed Case (OC) values

For the derivation of OC type values for intermediate sub-scores or total scores of composite scales, the following simple (non-model-based) approaches (could be) used for imputation of missing answers to single questions:

- best-case imputation: perform scoring as if the question had been answered in the sense of the best possible outcome;
- worst-case imputation: perform scoring as if the question had been answered in the sense of the worst possible outcome;
- linear up-scaling (for sum scores): in the first step, compute the (partial) sum score based on the available answer scores; in the second step, perform an up-scaling of this partial sum score to the full number of planned answers - the up-scaled score is given as:

$$\begin{aligned} &upscaled\ score \\ &\quad = \min score\ for\ all\ ansewers \\ &\quad + (\max sum\ score\ for\ all\ answers\ - \min sum\ score\ for\ all\ answers) \\ &\quad * \frac{(sum\ score\ for\ \text{filled}\ answers - \min sum\ score\ for\ filled\ answers)}{(\max sum\ score\ for\ \text{filled}\ answers - \min sum\ score\ for\ filled\ answers)} \end{aligned}$$

Illustrative example: if there are four questions in total, with answer scores ranging from 0 to 5 for the first two questions, and from 1 to 4 for the last two questions, and if only the first and the third question have been answered with scores of 5 and 3, respectively, then the partial sum score of 8 = (5+3) would be up-scaled to 16 = 2 + (18 - 2) * (8 - 1) / (9 - 1).

In the special case when the scores for all answers have the same range, linear up-scaling is equivalent to imputing the mean of the available answer scores for each of the missing answer scores.

For all scales/scores, approximately 80% of available answers have been decided to be the threshold to impute missing items.

6.6.1.1 Parkinson's Disease Sleep Scale-2 (PDSS-2)

If PDSS-2 is not completely answered, the missing questions will be imputed according to the linear upscaling as long as 12 of the 15 questions are available. If less than 12 questions of the 15 questions for PDSS-2 are available, the derived score PDSS-2 will be set to missing.

Three subscales of PDSS-2 "Disturbed sleep" (items 1–3, 8, and 14); "Motor symptoms at night" (items 4–6, 12, and 13); and "PD symptoms at night" (items 7, 9–11, and 15) will use the imputed items to do the analysis.

6.6.1.2 Nocturnal Hypokinesia Questionnaire (NHQ)

If NHQ is not completely answered, the missing questions will be imputed according to the linear upscaling as long as 8 of the 10 questions are available. If less than 8 questions of the 10 questions for NHQ are available, the derived score NHQ will be set to missing.

6.6.1.3 SCOPA-Sleep

NS (night-time sleep) subscale of B-section: 4-point Likert ranging from 0: “not at all” to 3: “a lot”; Additional item: 7-point Likert scale ranging from “slept very well” to “slept very badly”; and DS (daytime sleepiness) subscale of D-section: 4-point Likert scale ranging from 0: “never” to 3: “often”. The NS subscale score ranges from 0 to 15. The DS subscale score ranges from 0 to 18. Sum all the answers for each subscale to have the NS subscale score and the DS subscale score.

When more than one answer is ticked by the patient, the item score is considered missing. If only one score is missing in either the B- or D-sections of the scale, the score of the missing items is replaced by the non-weighted average of the non-missing items of that scale. If 2 or more scores are missing, a summary score is not calculated and considered missing.

6.6.1.4 Parkinson’s Disease Quality of Life Questionnaire (PDQ) -8

If PDQ-8 is not completely answered, the missing questions will not be imputed.

6.6.1.5 Epworth Sleepiness Scale (ESS)

If ESS is not completely answered, the missing questions will be imputed according to the linear up-scaling as long as 7 questions of the 8 questions are available. If less than 7 questions of the 8 questions for ESS are available, the derived score ESS will be set to missing.

6.6.1.11 Patient diary

This is clearly not a scale, but the question of handling missing partial data is virtually the same as for scales:

- In case of multiple entries for a half-hour, the worst case imputation will be applied.
- If a diary is not completely answered, the computation of percentages will be based on the set of half-hour intervals for which information is given (equivalent to linear upscaling or mean imputation for those half-hour intervals where no information is given) as long as at least 42 of the 48 half-hours intervals are available. If less than 42 half-hours of the 48 half-hours are available, the diary will be considered to invalid, and derived endpoints will be set to missing.

If derived endpoints are available for the two days (equivalent to two valid diaries), the derived endpoints for the visit will be the mean of the derived endpoints available for diaries (equivalent to compute the means for the available days).

If derived endpoints are only available for one day (equivalent to only one valid diary), the derived endpoints available will be set for this visit (equivalent to compute the means for the available days).

Intermediate variables will be computed for the calculation:

- The total on time period is the sum of half-hour periods that have been coded as "on" without dyskinesia, or as "on" with dyskinesia.

- The percent "off" during waking hours for day i with i=1, 2 (denoted DIAI) is equal to:

$$\%\ \text{"off" time duration} = \frac{\sum \text{"off"}\ half-hour\ period}{\sum \text{"off"}\ and\ \text{"on"}\ half-hour\ period}\ for\ day\ i \times 100$$

- "Off" time + "On" time duration (=∑"off" and "on" half-hour periods) for day i, where, the half-hours periods that are **either missing or "asleep" are not taken into account for the denominator**.

- Finally, the evaluation of percent "off" during waking hours for a visit (denoted DIAPO) will be calculated as the average of day 1 and 2, i.e. DIAPO is equal to arithmetic mean of DIA1 and DIA2.

- For each of the following times, the same derivation rules will be used to calculate the percent values:

  - "on without dyskinesia"

  - "on with dyskinesia"

Application:

If a patient reports the following in his/her diary for the visit (called X):

- Day 1: 44 half-hours filled in: 12 half-hours asleep/ 14 half-hours "off" / 4 half-hours "on without dyskinesia" / 14 half-hours "on with dyskinesia"

- Day 2: 45 half-hours filled in: 11 half-hour asleep/ 10 half-hours "off" / 8 half-hours "on without dyskinesia" / 16 half-hours "on with dyskinesia"

For Day 1, the diary is considered acceptable so the percent "off" during waking hours (called DIAPO1) will be DIAPO = 14/((14)+(4+14))*100=43.75%;

For Day 2, the diary is considered acceptable so the percent "off" during waking hours (called DIAPO2) will be DIAPO2 = 10/((10)+(8+16)) *100=29.41%;

So, for this visit X, the percent "off" during waking hours (called DIAPO) is: DIAPO= (DIAPO1+DIAPO2)/2=(43.75%+29.41%)/2=36.58%.

6.6.2 Other

6.6.2.1 Handling of partial and missing Adverse Event (AE) and dates

Missing or incomplete AEs' start dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (2).

6.6.2.2 Handling of partial and missing Concomitant Therapy (CT) dates

The aim of the algorithm is to apply the "worst case scenario", i.e., to allocate the CT to the "On-Treatment" period.

6.6.2.3 Handling of partial trial indication date

When deriving time since trial indication variable, then the following rule will be applied: If day is missing then day='15'. If month and day are missing then month='07' and day='01'. If this substitution results in a negative duration, then the duration is set to 0 year.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

It is initially not planned to work on calculated visits; however timing deviations will be carefully checked during MQRMs. If there are too many important timing deviations then the following rules will be applied (this decision will be taken at the latest during the final RPM).Primary and secondary efficacy analyses will be based on calculated visits which will be labelled by 'Week X' in tables, listings and figures. A calculated visit is a visit that corresponds to a time interval based on relative days. The calculated visits form a set of exhaustive, non-overlapping time intervals covering the entire duration of the trial. Calculated visits will usually have a one-to-one correspondence with planned visits.

If two or more data points of a patient fall into the same interval, the following rules will be used:

- Pre-treatment period: use the last value
- Treatment period: use the closest value to the planned day
- Post-treatment period: use first value

In case where two visits fall in the same interval and at equal distance to the planned visit, the first one will be taken for the analysis.

The following first table presents the visit structure according to the study flowchart:

Table 6.7: 1 Visit structure

Trial Period	**Screening**	**Random**	**Treatment**										
			Flexible up-titration phase							**Maintenance**			**Follow up**
Visit	**V1**	**V2**	TC1	**V3**	TC2	**V4**	TC3	TC4	TC5	**V5**	**V6**	**V7**	**V8**
Week(s)	-2 to -1	0	1	2	3	4	5	6	7	8	12	18	NA
Day(s)	-14 to-3	0	7 ±2	14 ±2	21 ±2	28 ±2	35 ±2	42 ±2	49 ±2	56 ±3	84 ±3	126 ±3	Last dose+2 +3
Description	Screen	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 18	End Taper

The following tables shows how measurements will be assigned as calculated visit based on the day (relative to first study drug intake) on which measurements were made. Below are different patterns for interval definition of different types of endpoints:

- PDSS-2, NHQ, SCOPA-sleep, EMO, ESS, (refer to Table 6.7: 2)
-
- PDQ-8, (refer to Table 6.7: 4)
- PGI-I (refer to Table 6.7: 5)
- CGI-I (refer to Table 6.7: 6)

Table 6.7: 2 Definitions of calculated visits

Visit No	Planned day	Interval definition		Visit description	Example	
		From	To		Actual day	Calculated visit
V2	0	-∞	0	Baseline	0	V2
V3	14	1	20	Week 2	17	V3
V4	28	21	41	Week 4	28	V4
V5	56	42	69	Week 8	54	V5
V6	84	70	104	Week 12	100	V6
V7	126	105	+∞	Week 18	120	V7

The “Actual day” column lists an example of actual days. The “Calculated visit” column shows how the algorithm would be applied to these actual days. In the example, actual day 3 and 17 fall in the same interval from day 1 to 20, so they should both be categorized under calculated visit 3 (Week 2). By default, the value for day 17 will be used for the visit 3 because it is the closest value to the planned day.

In accordance with the corresponding rules for safety data, measurements up to 2 days (inclusive) after last intake of study medication (during up-titration, maintenance or down-titration periods) will be considered as on-treatment for the statistical analysis. This decision might be modified at the final RPM at the latest.

Even if we do not use the calculated visit for the analysis, a variable "Study Day" will be added for all over time data in the analysis data set, representing the time since first drug administration. In any case, the VISIT 8 for prematurely discontinued patients will need to be re-structured following those rules.

Table 6.7: 3 Interval definition

Visit No	Planned day	Interval definition		Visit description
		From	To	
V2	0	-∞	0	Baseline
V4	28	1	41	Week 4
V5	56	42	90	Week 8
V7	126	91	+∞	Week 18

Table 6.7: 4 Interval definition

Visit No	Planned day	Interval definition		Visit description
		From	To	
V2	0	-∞	0	Baseline
V5	56	47	90	Week 8
V7	126	91	+∞	Week 18

Table 6.7: 5 Interval definition for PGI-I

Visit No	Planned day	Interval definition		Visit description
		From	To	
TC1	7	0	9	Week 1
V3	14	10	17	Week 2
TC2	21	18	24	Week 3
V4	28	25	31	Week 4
TC3	35	32	38	Week 5
TC4	42	39	45	Week 6
TC5	49	46	52	Week 7
V5	56	53	69	Week 8
V6	84	70	104	Week 12
V7	126	105	+∞	Week 18

Table 6.7: 6 Interval definition for CGI-I

Visit No	Planned day	Interval definition		Visit description
		From	To	
V4	28	26	48	Week 4
V5	56	49	90	Week 8
V7	126	91	+∞	Week 18

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

Baseline refers to the last assessment of a variable prior to first trial drug intake.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic and baseline characteristics will be displayed for TS by treatment group and for the total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and medication on-treatment period will be displayed for TS population. Only descriptive statistics are planned for this section of the report.

Concomitant diseases will be displayed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term (PT) by treatment group and for the total. Concomitant non PD therapy medication will be displayed by Anatomical Therapeutic Chemical level 2 (ATC2) and Preferred Names (PNs) respectively by treatment group and for the total. A frequency table will be provided for the concomitant Anti-PD therapy and added (i.e., new added) Anti-PD therapies with their ATC4 and PN.

Tables will also describe the concomitant L-Dopa therapies. The L-Dopa daily dose/ L-Dopa equivalent daily dose and the percentage of patients with L-Dopa dose/ L-Dopa equivalent daily dose ≤400mg or >400mg will be described.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The compliance will be displayed separately by visit interval and total. Treatment compliance will be displayed for the TS population.

7.4 PRIMARY ENDPOINT(S)

The analysis of the primary endpoint will be conducted in accordance with Section 7.3.1 of the CTP. The statistical model will be as follows:

$$y_{ijk} = \beta_j S_i + \tau_{ik} + e_{ij}$$
$$e_{ij} \sim N_z(\mathbf{0}, \mathbf{\Sigma})$$

y_{ijk}= change from baseline in PDSS-2 for subject i at visit j receiving treatment k,
S_i= the baseline PDSS-2 total score of subject i, i=1, 2, …
β_j= coefficient of baseline effect at visit j
τ_{jk}= the effect of treatment k at visit j, j= 1, …, Z and k = 1, ..,Y
e_{ij}= the random error associated with the j^{th} visit of the i^{th} subject. Errors are independent between subjects.
$\mathbf{\Sigma}$= an unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Tests will be based on least-squares means using a two-sided α = 0.05 (two-sided 95% confidence intervals).The primary treatment comparison will be the contrast between treatments at the endpoint visit.

The primary analysis will be performed on FAS. The sensitivity analysis will be performed on PPS.

The only stratification factor, i.e., site, will be excluded from the primary model, because it is simply be done for the convenience of running the trial ("organizational strata") due to the manual envelop randomization. It is performed to minimize the amount of unused supplies at each site and thereby simplify stock control. Therefore, site needs not be included per default in the primary analysis model.

In the event of non-convergence, the following methods will be attempted (in order) to overcome it:

1. Add the ‘singular=1e-10’ option in the model statement – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).
2. Set ‘maxiter=100’ in the Proc Mixed statement – This increases the number of convergence iterations used from a default of 50.
3. Set ‘scoring=4’ to specify use of the Fisher scoring algorithm in the first 4 iterations.
4. Include the statement ‘performance nothread’ – this removes multi-threading from the calculations.
5. Provide starting values for covariance parameters using a ‘parms’ statement. Estimates will be obtained from by prior knowledge or possibly by first running the model using a simpler covariance matrix.
6. Use a simpler covariance matrix: Should none of the previous methods work, the covariance matrix will be changed from unstructured to Toeplitz with heterogeneous variances (TOEPH). Should this also not converge, a standard Toeplitz matrix (TOEP) will

be fitted. Finally, if convergence still does not occur, then an order-1 autoregressive matrix (AR(1)) will be fitted.

The primary model will be also evaluated by subgroup (refer to section 6.4) and on the PPS population.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

Continuous endpoints will be analyzed using a MMRM model with the same effects as the primary endpoint, but using the respective baseline of the continuous endpoint as covariate.

Logistic regression analyses will be performed with treatment and baseline (if baseline was measured) as the independent variables.

7.7 EXTENT OF EXPOSURE

Extent of exposure will be displayed for the TS. The standard descriptive statistical parameters on duration and doses of study drug administration will be calculated and displayed separately for all treatment groups.

Frequencies will be also prepared for the following categories : < 1 week, 1 - <4 weeks, 4 - <8 weeks, 8 - <12weeks, and >=12 weeks. And mean final dose and cumulative dose will be calculated and the final dose distribution for daily doses and categories (low, median, high) will be displayed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS population.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, and outcome).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (2, 3).
The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till last drug intake + 2 days will be assigned to the randomized treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after the last drug intake +2 days will be assigned to 'post-treatment' (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarized by treatment, primary System Organ Class (SOC) and Preferred Term (PT) (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for some kinds of adverse events.

The SOCs will be sorted alphabetically; PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4).

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

Not applicable.

7.8.5 Others

The number and frequency of MMIDI, MMIDI for compulsive sexual behaviour, for compulsive buying, and for pathological gambling and abnormal behaviour will be displayed.

8. REFERENCES

1.	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
4.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
Initial	**22-Jun-18**		None	This is the initial TSAP with necessary information for trial conduct
Final	**25-Sep-19**		None	This is the final TSAP with all information for trial phase I conduct